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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/458,610	12/10/1999	ELIZABETH G. NABEL	8642/88	9076

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/458,610	NABEL ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *106-146* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *106-146* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/24/05 has been entered. Applicant's amendment and response also received on 2/24/05 have been entered. Claims 1-105 are canceled. New claims 143-146 have been added. Claim 106-146 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office actions.

Claim Rejections - 35 USC 112

The rejection of pending claims 109-119 and 121-142 under 35 U.S.C. 112, first paragraph, for lack of enablement is **maintained**. The rejection of claim 120 is withdrawn in view of applicant's amendment of the claim to depend on claim 106. Applicant's amendments to the claims and arguments have been fully considered but have not been found persuasive in overcoming the following grounds of rejection of the claims for reasons of record discussed in detail below.

The applicant argues the examiner did not consider the Nabel Declaration and that the Office has ignored the data because p27 was not known as of the priority date of the instant invention (1989). The present response also substantially reiterates the arguments previously presented which were addressed in full in the previous office action. In response to these arguments, the applicant is specifically directed to the previous office actions. In particular, the last office action, mailed on 8/25/04, clearly provided a detailed discussion of the data provided in the Nabel Declaration. The previous office actions also clearly indicated that contrary to applicant's argument, the Nabel Declaration was considered in its entirety. However, as discussed in detail, the declaratory evidence was not found to enable to breadth of the pending claims. The relevant portions of the previous office action are provided below for applicant's convenience. Applicant's amendments to the claims have also been addressed below.

The applicant states that the courts do not prohibit operativeness from being demonstrated by actual reduction to practice at any time. In response, the MPEP section 2164.05(a) clearly states that the specification must be enabling as of the filing date. In this case, the effective filing date is 1989. While the applicant is correct that post-filing evidence may be provided to demonstrate that the invention works, the MPEP clearly states, " However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention" (MPEP 2164.05). *Quigg v. Gould*, as cited by applicants, concurs with

the MPEP, "post-filing evidence is relevant to enablement if it proves that the invention works as broadly as claimed". The data presented in the Nabel declaration does not meet the standard set forth in the MPEP or in *Quigg v. Gould*. The p27 gene was not known in the prior art as of 1989. The gene was not discovered until 1994. Thus, the material used in the experiments described in the declaration was not described in the specification or well known to one of skill in the art. Further, even as amended, the claims as written are broad and read generally on the expression of any recombinant protein by vascular cells implanted into a host mammal, and the treatment of any ischemic disease in a human patient by the installation of transformed endothelial, smooth muscle, or parenchymal cells. The declaratory evidence is not commensurate in scope with the claimed invention. The single example provided in the declaration demonstrates that the expression of p27 from vascular smooth muscle cells delivered by catheter to the femoral artery can inhibit catheter-induced neointimal hyperplasia. However, as noted above, the methods claimed read on the treatment of any type of ischemic condition in a patient by the instillation of transformed vascular cells. The diseases recited in the specification include diabetes, liver disease, hypercholesterolemia, malignancy, cardiomyopathy and peripheral vascular disease, all of which qualify as an "ischemic condition". The diseases specifically recited in the claims include cardiovascular disease in general, and ischemic cardiomyopathy; and the sites for installation of the cells includes the heart, kidney, liver and bowel. The diseases listed in the specification and specifically recited in the claims have substantially different etiology than injury induced neointimal hyperplasia, and are likely caused by substantially different factors, both genetic and environmental. Further, the candidate proteins recited in the specification and now recited in claims 109 and 116 as putative therapeutic agents for treating these diseases are

all substantially different proteins with different biological properties and activities not related to p27. p27 is a cell cycle inhibitor that acts to inhibit cyclin-CDK complexes. Urokinase and tPA, now recited in the claims, are proteases which act to convert plasminogen to plasmin. TNF and TGF are both inflammatory cytokines. As such, a nexus between the activity of the cell cycle inhibitor p27 expressed from transformed vascular smooth muscle cells on neointimal hyperplasia and the activity of any other substantially different proteins expressed by any vascular cell, or endothelium or parenchymal cells on injury induced neointimal hyperplasia or other types of ischemic diseases which differ substantially from injury induced neointimal hyperplasia cannot be made. As such, the declaratory data does not overcome the lack of enablement for the breadth of the methods as claimed.

The applicant further argues that, "Similar to *In re Strahilevitz*, in the present situation when various art references are considered in combination with the specification, the specification enables one of ordinary skill in the art to practice the claimed invention". The teachings provided in the specification have been discussed in detail in previous office actions and have not been found sufficient to enable the breadth of the invention as claimed. In short, while the specification does in fact disclose a number of putative therapeutic proteins that could be used in applicant's methods, no data regarding the actual activity of these putative therapeutic proteins when expressed *in vivo* according to the instant methods has been presented in the specification. As noted in previous office actions, the specification's working examples demonstrate the transfection of endothelial cells with a vector encoding lac-Z, and the installation of these cells by balloon catheter to blood vessels *in vivo*. The specification reports that the endothelial cells expressed detectable levels of beta-galactosidase following

transplantation. The specification also states that expression could be detected for approximately six weeks. However, the specification does not correlate the level of beta-galactosidase with any therapeutic effect on any disease symptom or teach that the expression of similar levels of any other protein, such as FGF or tPA, for similar periods of time from transplanted endothelial cells or any other type of vascular cell would result in any effect on any cardiovascular condition such as atherosclerosis, restenosis, or heart disease, or any other type of ischemic in any organ including liver, kidney, or bowel.

The relevance of the supporting references previously cited by the applicants was also addressed in the previous office action and is reiterated as follows. The applicant has previously cited the following references as support in the prior art for enablement of the instant invention: St. Louis et al., Selden et al., Nabel et al., U.S. Patent 5,661,133, Jacob et al., Cuevas et al., Hayek et al., and Wilson et al. St. Louis et al. and Selden et al. both disclose murine fibroblasts modified to express either human factor IX or human growth hormone respectively. Neither reference adds to the enablement of the instant claimed methods at the time of filing. St. Louis et al. discloses a substantially different method comprising the implantation of collagen embedded fibroblasts expressing recombinant human factor IX embedded into the epidermis. Further, St. Louis et al. does not demonstrate any therapeutic effect resulting from the implantation. St. Louis et al. only teaches that human factor IX expression was detected and that levels of human factor IX rapidly decreased due to murine antibody reactivity against the human protein. Thus, St. Louis uses a non-analogous method, i.e. fibroblasts embedded in collagen, and does not demonstrate any treatment effect on any disease. Selden et al. is less relevant. Selden et al. only teaches the expression of human growth hormone in murine fibroblasts *in vitro*. The *in vivo* data

discussed in Selden et al. was generated in transgenic mice. The presence of the human growth hormone gene in the germline of a transgenic mouse and the subsequent expression of the gene during the life of the mouse is not analogous to the site specific installation of transformed endothelial, smooth muscle, or parenchymal cells. While Selden et al. shows that the continuous expression of the hGH transgene in mice can affect growth, Selden et al. does not teach or suggest that cells transformed to express the human growth hormone could have the same effect.

Hayek et al., Cuervas et al., and Jacob et al. all teach the direct administration of recombinant protein, not the administration of cells transformed to express the protein. Please note that Hayek et al. and Cuervas et al. have been provided as an abstract only and have been considered as such. Hayek et al. teaches the implantation of slow release beads containing bFGF under the kidney capsule. While Hayek et al. reports that bFGF has some angiogenesis activity, the method of Hayek et al. is not analogous to the instant invention and does not demonstrate that the skilled artisan would have expected that transformed cells would be able to successfully express the same amount of protein for the same length of time. Cuervas et al. used alzet osmotic pumps to deliver bFGF to the intrarticular space. Again, this is not an analogous method and Cuervas et al. does not provide any guidance on the administration of transformed cells. Jacob et al. teaches the intraperitoneal injection of TNF-alpha protein 3X/week for 12 weeks in NOD mice. Like Hayek and Cuervas, Jacob et al. does not teach or suggest implanting transformed cells or provide any guidance that a transformed cell would be able to continuously express a therapeutic level of protein for a period of time sufficient to treat diabetes or any other type of disease.

The Nabel papers and the Nabel patent, U.S. Patent No. 5,661,133, are all post-filing references which teach the direct administration of nucleic acid encoding a protein directly to an artery. Again, this is not an analogous method to the claimed method. Further, as these references were published several years after the effective filing date, they do not represent the state of the art at the time of filing.

Finally, Wilson et al. teaches the temporary amelioration of hyperlipidemia by intraportal administration of hepatocytes expressing recombinant human LDL receptor. While this reference is most relevant to the claims as written, this reference was filed after the effective filing date of the application. As a post-filing reference, it does not establish the state of the art at the time of filing. As evidence of reduction to practice after the filing date of the application, the Wilson et al. experiments are not analogous as they use transformed hepatocytes, which are substantially different from the cell types recited in the claims, i.e. vascular cells, endothelial, smooth muscle, or parenchymal cells. The Wilson et al. results are not commensurate in scope with the claimed methods and do not teach or suggest that other cell types could substitute for hepatocytes in treating hyperlipidemia in the liver. Nor does Wilson et al. teach or suggest that other types of transformed cells could be used to treat other types of disease.

Taken as a whole, none of the references cited by the applicants exemplifies the instant methods as claimed, or teaches that the implantation of transformed vascular cells would be capable of expressing sufficient levels of a therapeutic protein for a sufficient length of time to treat any disease in any mammal, including a human. The applicant appears to be arguing that many therapeutic proteins capable of treating disease were known in the prior art. However, the existence of "therapeutic" proteins is not the issue. The issue is the lack of enablement for

treating disease by expressing the therapeutic protein in transformed vascular cells implanted into a mammal or human. The prior art references cited do not add to the guidance provided by the specification regarding site specific installation of transformed vascular cells or provide any indication that the skilled artisan would have considered the treatment of disease by the administration of transformed vascular cells to be predictable. The post-filing references cited do not demonstrate the reduction to practice of the invention after the effective filing date as the experiments discussed in the post-filing references are not analogous to the instant methods as claimed or commensurate in scope with claims as written. Thus, the office does not find that the evidence provided, alone or in combination with the guidance provided by the specification enables the instant methods as claimed.

It is also noted that the previous office actions have demonstrated that at the time of filing, the skilled artisan did not consider the expression of therapeutic levels of protein for the treatment of disease as predictable. The references cited in the previous office action, Verma et al., Ledley et al., and Orkin et al., teach the unpredictability of achieving therapeutic levels of expression of a transgene in vivo by either direct or indirect administration of a recombinant vector or cells transduced/transfected with a recombinant vector. Thus, contrary to applicants assertion, the skilled artisan would not have predicted at the time of the effective filing date of the instant application that the expression of any level of a putative therapeutic protein from transduced endothelial, smooth muscle or parenchymal cells for any length of time would result in a therapeutic effect on the disease to be treated.

Finally, the previous office actions have analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the

prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of the skilled artisan, and 8) the breadth of the claims, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement for the scope of the instant methods. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). 35 U.S.C. 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Therefore, in view of the substantial functional differences between putative therapeutic proteins recited, the substantial differences between ischemic disease such as injury induced intimal hyperplasia, peripheral vascular disease, cardiovascular disease, ischemic conditions of the liver, kidney, or bowel, the art-recognized unpredictability in achieving therapeutic levels of gene expression *in vivo* capable of treating a disease, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

As a final note, applicant's request for an affidavit under 37 CFR 1.104(d)(2) is misplaced since the rejection of record is not based on the examiner's "personal knowledge". Rather, the rejection of record is based on the well documented state of the art of gene therapy,

which has been supported by the citation of several references from the art, the nature of the invention, the breadth of the claims, and the evaluation of the teachings of applicant's specification and supporting evidence as required by 35 U.S.C. 112. The rejection of record has been set forth in substantial detail in the previous office actions and largely reiterated above.

Double Patenting

The rejection of pending and new claims 106-109, 114-118, 121-131, 136, 142-146 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-14 of U.S. Patent No. 6,203,991 (3/20/01), the '991 patent, is maintained. While the applicant states that they disagree with the grounds of rejection, no specific arguments traversing the rejection are presented. However, the applicants state their intention to file a terminal disclaimer upon the allowance of the rejected claims. As a terminal disclaimer has not yet been filed, the rejection of record stands.

Applicant is advised that should claims 106-108 be found allowable, new claims 143-146 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER